REMARKS

Claims 12-61 are pending in the application. Support for the amendments to claims 30 and 36 and newly added claims 50 and 51 in the recitation of the lipids and cationic lipids can be found at *inter alia*, page 20 in the specification. Support for newly added claims 52 to 61 in the recitation of host cells can be found at *inter alia*, page 6 in the specification. Further, implicit support for "eukaryotic" cell can be found in the general concept of the invention in which transfection techniques are used to introduce the large circular single stranded nucleic acid to eukaryotic cells so that target specific inhibition of gene expression is detected. Thus, no new matter has been inserted into the application. No new issue is raised requiring further search or consideration. Entry of the amendments to the claims is respectfully requested.

Claim Objections

Claims 46 and 47 have been objected to for lacking an article "a" before "liposome". The amended claims 46 and 47 recite "a" before "liposome". Accordingly, this objection has been overcome.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 22 and 34 have been rejected under 35 U.S.C. § 112, Second Paragraph, as being indefinite for lacking antecedent basis for various recited language. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Claim 22 has been amended to insert antecedent basis for "said gene." And claim 34 has been amended to depend from claim 33 to provide antecedent basis for the objected to phrase. Accordingly, this rejection has been overcome.

Rejection Under 35 U.S.C. § 102(b) Over Hellmann (Virology. Vol. 143, pp. 295-303 (1985))

Claims 30, 31, 33-37 and 39 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Hellmann. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Hellmann

Hellmann discloses an M13 molecule with a Tobacco Vein Mottling Virus (TVMV) insert sequence. Hellmann further discloses performing DNA:RNA hydridization assays with the M13 molecule in a reticulocyte lysate cell-free translation system, the so called hybrid-arrested translation system.

Hellmann fails to disclose or suggest mixing the M13 molecule with a eukaryotic cell transfection effective composition containing lipids such as cationic lipids or liposomes because Hellmann's assays with the M13 molecule is conducted entirely in a cell-free system, and there is no disclosure or suggestion found in Hellmann to combine the M13 molecule with any eukaryotic cell transfection reagent for introducing the M13 molecule into a cell.

The Examiner is reminded that in order to reject a claim under §102, each and every element in the claim must be disclosed in the cited reference. In the present situation, Hellmann fails to disclose or suggest including a transfection effective carrier comprising a lipid as in the claimed invention. Therefore, Hellmann fails to anticipate the claimed inventive composition.

Rejection Under 35 U.S.C. § 102(b) Over Moon (J. Biol. Chem. 275(18), pp. 4647-4653 (2000))

Claims 22 and 42 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Moon. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Moon discloses a ribbon-type antisense oligonucleotide. However, Moon fails to disclose or suggest the presently claimed inventive composition, which is directed to a large circular single-stranded nucleic acid molecule, which is at least about 3,000 nucleotides long and/or comprises a recombinant bacteriophage or phagemid genome. Therefore, Moon fails to anticipate the presently claimed invention.

Rejection Under 35 U.S.C. § 102(b) Over LaPlante (Biochem J. Vol. 348, pp. 189-199 (2000))

Claims 23, 30-32 and 42 have been rejected under 35 U.S.C. § 102(b) as being anticipated by LaPlante. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

LaPlante discloses an antisense cDNA for the gene encoding CHERP. However, LaPlante fails to disclose or suggest the presently claimed inventive composition, which includes a large circular single-stranded nucleic acid molecule, which is at least about 3,000 nucleotides long and/or comprises a recombinant bacteriophage or phagemid genome.

In the Office action at page 5, second full paragraph, the Examiner appears to interpret the phrase "comprising . . . a single-stranded nucleic acid molecule" recited in claims 23, 30 and 42 to read on a double-stranded nucleic acid molecule because of the use of the legally defined open-ended term "comprising". Applicants disagree with this interpretation. Applicants submit that a person of ordinary skill in the art would not consider the phrase "comprising single-stranded" to include "double-stranded". This is especially true given the nature of the invention.

The invention is directed to a single-stranded nucleic acid which is capable of hybridizing to its complement nucleic acid. Since this is the essence of the patent application, a person of ordinary skill in the art reading the claim in view of the specification would not understand "comprising single-stranded" to mean double-stranded. As examples, the Examiner's attention is directed to Claim 105 of U.S. Patent No. 6,677,121 and Claim 1 of U.S. Patent No. 6,423,492, in which a distinction is recognized between double stranded and single stranded nucleic acids. Accordingly, removal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103(a) Over Hellmann in view of Hu '062 (U.S. Patent No. 6,107,062)

Claims 22, 23, 46 and 47 have been rejected as being obvious over Hellmann in view of Hu '062. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Basic considerations which apply to obviousness rejections

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). (MPEP 2141).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant"s disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). MPEP 2142.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee,* 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to

the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). MPEP 2143.

In order to establish *prima facie* obviousness of the invention over the cited references, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. The Federal Circuit has produced a number of decisions overturning obviousness rejections due to a lack of suggestion in the prior art of the desirability of combining references, as discussed in the aforementioned section. In the present situation, the Examiner has failed to establish *prima facie* obviousness of the present invention over Hellmann and Hu '062.

Hellmann's disclosure and the problem to be solved.

Hellmann discloses an M13 construct with a Tobacco Vein Mottling Virus insert sequence, which is used to create DNA:RNA hybrid as used in an *in vitro* cell-free hybrid arrest assay. Hellmann is focused on developing an assay system to determine the origin of the polypeptide product encoded by the 5'- terminal region of the RNA of the potyvirus. Hellmann is further focused on precisely mapping the potyviral proteins and understanding the translational mechanisms by which they are produced. Hellmann states that single-stranded DNAs derived from plasmids containing approximately 95% of the sequences of TVMV RNA arrest the translation of specific portions of TVMV RNA and discovered that synthesis of P75 is initiated near the 5' terminus (paragraph bridging pages 23-24). To solve the problem of understanding the translational mechanisms of potyvirus, Hellmann chose to employ a cell-free translation system using single-stranded DNA fragments obtained from M13, which contains the TVMV inserts because "initial attempts to perform hybrid-arrested translation experiments using double-

stranded recombinant plasmids were unsuccessful due to rapid annealing of the DNA strands under the hybridization conditions use." (Page 25, paragraph bridging left and right columns).

Hellmann's research focus is on using a single-stranded DNA in cell-free hybrid arrested translation experiments because Hellmann is interested in the problem of solving the translational machinery of potyvirus for which the cell-free system is a more helpful experimental methodology than cell-based methodology. Accordingly, Hellmann fails to disclose or suggest transfecting any eukaryotic cell. Further, Hellmann fails to disclose or suggest transfecting any cell with a single-stranded DNA.

Hu '062's disclosure and the problem to be solved.

Hu '062 is relied on for the disclosure of a plasmid that expresses several target specific antisense RNA, which inhibits the target gene expression. Hu '062's research focus uses a cell-based system in which the cells are transfected with a double-stranded plasmid. Hu '062 is mainly concerned with optimizing expression of its antisense RNA producing method and its effectiveness within a cell. Hu '062 is not concerned at all with any cell-free system. Hu '062 is not concerned with any translational mapping that would warrant turning to a reference like Hellmann for guidance. To Hu '062, the Hellmann reference would be outside the purview of its research and therefore, Hu '062 would not have considered the Hellmann reference to be of any help in Hu '062's cell based target gene expression inhibition methods.

Hellmann and Hu '062 are not combinable with each other.

Applicants submit that the Hellmann reference and the Hu '062 patent fail to be combinable with each other. Hu '062 is firmly focused on inhibiting target gene expression by the expression of exogenously introduced plasmid DNA that expresses antisense RNA. Hu '062's research field is firmly in the realm of transfecting cells, assaying for gene expression

within cell background, and assaying for changes in cell morphology. The methods and techniques employed richly revolve around cell cultures and assays using live organisms, which extend to therapeutics and treatment of disease, specifically AIDS. This is in stark contrast to the Hellmann reference, which is directed to a cell-free assay system that employs a single-stranded M13 phage construct to determine the translational mechanism of the potyvirus. Hellmann fails to disclose any information regarding any cell-based type of system. And a person in the art of target gene inhibition by expression of antisense RNA would not look to a cell-free assay system for guidance in solving its problems.

Since the purposes for which each reference uses either the single-stranded or double-stranded form of either the phage or the plasmid vector are divergent, a person of ordinary skill in the art reviewing the Hellmann reference would not be motivated to consider using a plasmid DNA expressing antisense RNA to assist in solving the hybridization problem discussed in the Hellmann reference. And *vice versa*, a person in the cell-based antisense therapy field would not be motivated to consider using a single-stranded M13 vector construct of Hellmann in solving its therapeutic focus, as there is simply no motivation found in either reference to combine these two references. Accordingly, the presently claimed invention is not obvious over the cited references.

Moreover, as the present claims 46 and 47 stand rejected over Hellmann and Hu '062, Applicants submit that Hellmann fails to disclose or suggest transfecting the single-stranded M13 into a eukaryotic cell, and Hu '062 fails to disclose or suggest transfecting a cell with a single-stranded nucleic acid. Thus, Hu '062 fails to remedy the deficiencies in Hellmann. Accordingly, claims 46 and 47, directed to a large circular single stranded nucleic acid molecule comprising a transfection effective carrier comprising a liposome are not obvious over Hellmann and Hu '062.

Rejection Under 35 U.S.C. § 103(a) Over Hellmann in view of Moon and LaPlante

Claims 38, 46 and 47 have been rejected as being obvious over Hellmann in view of Moon and LaPlante. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Hellmann is discussed above; Moon is discussed above; and LaPlante is discussed above.

Applicants submit that the Examiner has failed to establish *prima facie* obviousness of the presently claimed invention over the cited references. Applicants note that Hellmann discloses a single-stranded M13 for use in a cell-free hybridization system. Hellmann fails to disclose a single-stranded full-length gene and a liposome transfection system.

LaPlante discloses an antisense cDNA and its transcript. However, LaPlante fails to remedy the deficiencies of Hellmann because LaPlante fails to discloses or suggest replaceability of the M13 disclosed in Hellmann with the single-stranded RNA transcript. Further, there is no motivation for Hellmann to look to La Plante to solve its cell-free hybrid arrest system. Accordingly, LaPlante is not combinable with Hellmann. Thus, LaPlante fails to be applicable to the presently claimed invention.

Moon discloses RiAS complexed with a liposome. However, there is no disclosure or suggestion present in Hellmann for a need for a liposome in its assay system because Hellmann is satisfied with its system and Hellmann has no purpose or reason for transfecting any cell with its single-stranded M13. Therefore, Moon is not combinable with Hellmann. Further, Moon fails to disclose or suggest that the liposome transfection system will be functional with a single-stranded nucleic acid which is at least about 3,000 bases long or a phage.

Accordingly, the presently claimed invention is not obvious over the cited references.

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. **502486** for any fees required under 37 CFR §§ 1.16 and 1.17 that are not covered, in whole or in part, by a credit card payment enclosed herewith and to credit any overpayment to said Deposit Account No. **502486**.

Respectfully submitted,

JHK Law

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